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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/079,241	02/20/2002	Holly Hogrefe	25436/2155	7186

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EXAMINER
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HUTSON, RICHARD G

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 11/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

10/079,241

**Applicant(s)**

HOGREFE ET AL.

**Examiner**

Richard G. Hutson

**Art Unit**

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☐ Responsive to communication(s) filed on 11 August 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 64-94 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 64-94 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

Applicant's amendment of claims 64, 65, 68, 73, 76 and 85, in the paper of 8/11/2006, is acknowledged. Claims 24-27 and 31-68, 70-94 are at issue and are present for examination.

Applicants' arguments filed on 8/11/2006, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 24-27 and 31-63 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 64-94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 64-94 are indefinite in that they are drawn to a mixture comprising a first enzyme that comprises "a polymerization activity of a DNA polymerase or reverse transcriptase...". It is indefinite as to what type of activity applicants intend to be encompassed by "a polymerization activity". One of skill in the art

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knows that polymerases and reverse transcriptases have various polymerization activities, such as substrate binding, catalytic and processive activities etc...

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 64-94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 64-94 are rejected under this statute because the limitation of claim 64 that both the first and second enzyme be a Archaeal DNA polymerase or a mutant Archaeal DNA polymerase is not supported by the specification at the time of filing and is thus considered new matter.

Claims 64-94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

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Claims 64-94 are directed to all possible enzyme mixtures comprising a first enzyme and a second enzyme wherein said first enzyme is any enzyme which comprises any polymerization activity of a DNA polymerase or reverse transcriptase and said second enzyme is any mutant DNA polymerase comprising a mutation selected from the group consisting of Y410, T542, D543, K593, Y595, Y385, G387 and G388. The specification, however, only provides those representative species in which the first enzyme is a DNA polymerase or a reverse transcriptase and said second enzyme is a Pfu DNA polymerase which comprises the amino acid sequence of SEQ ID NO: 19, with a mutation selected from the group consisting of Y410, T542, D543, K593, Y595, Y385, G387 and G388, encompassed by these claims. There is no disclosure of any enzymes beyond DNA polymerases and reverse transcriptases, that have DNA polymerization activity and applicants have not described a particular structure to function/activity relationship in the disclosed species (See also 112 second paragraph rejection). Given this lack of additional representative species of those enzymes beyond DNA polymerases and reverse transcriptases that have DNA polymerization activity, as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at [www.uspto.gov](http://www.uspto.gov).

Claims 64-94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an enzyme mixture comprising a DNA polymerase and a Reverse Transcriptase and a Pfu DNA polymerase which comprises the amino acid sequence of SEQ ID NO: 19 with a mutation selected from the group consisting of Y410, T542, D543, K593, Y595, Y385, G387 and G388, does not reasonably provide enablement for any enzyme mixture comprising first enzyme comprising a polymerization activity of a DNA polymerase or reverse transcriptase and a mutant Archaeal DNA polymerase comprising one or more mutations at positions Y410, T542, D543, K593, Y595, Y385, G387 and G388 of *Pfu* DNA polymerase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 64-94 are so broad as to encompass any enzyme mixture comprising any enzyme having any polymerization activity of a DNA polymerase

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or reverse transcriptase and any mutant Pfu DNA polymerase comprising one or more mutations at positions Y410, T542, D543, K593, Y595, Y385, G387 and G388. The claims rejected under this section of U.S.C. 112, first paragraph, do not place any structural limits on those enzymes having "a polymerization activity" or the claimed mutant DNA polymerases. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to those instantly disclosed mutant Pfu DNA polymerases comprising the amino acid sequence of SEQ ID NO: 19, further consisting of a mutation at a position selected from the group consisting of Y410, T542, D543, K593, Y595, Y385, G387 and G388.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments enzyme having a polymerization activity of a DNA polymerase or a reverse transcriptase or any of the specified mutant DNA polymerases, because the specification does not establish: (A) regions of the proteins structure which may be modified and the resulting effect on their activity; (B) the general tolerance of polymerases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a polymerase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the desired and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in *The Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those enzyme mixtures of the claimed genus.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any enzyme mixture comprising an enzyme having any polymerization activity of a DNA



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polymerase or a reverse transcriptase and any mutant DNA polymerase with the specified mutations. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)).

Without sufficient guidance, determination of those mutant polymerases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

See In re Wands 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 64-66, 68, 71, 73, 75, 79, 85, 87, 89, 91 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barnes et al. (U.S. Patent No. 5,436,149) and Komori et al. (Protein Engineering, Vol 13. No. 1, pages 41-47, 2000).

Barnes teach a number of thermostable DNA polymerase mutants and formulations of the taught DNA polymerases and other thermostable DNA polymerases, which formulation of enzymes are capable of efficiently catalyzing the amplification by PCR of unusually long and faithful DNA products. Barnes specifically teach a formulation of thermostable DNA polymerases comprising at least one thermostable DNA polymerase lacking 3'-exonuclease activity and at

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least one thermostable DNA polymerase exhibiting 3'-exonuclease activity, wherein the thermostable DNA polymerase exhibiting 3'-exonuclease activity is a variant of the *Pfu* DNA polymerase wherein the DNA polymerase activity of said *Pfu* DNA polymerase has been diminished or inactivated.

Komori et al. teach the functional interdependence of DNA polymerizing and 3'-5' exonucleolytic activities in *Pyrococcus furiosus* (*Pfu*) Polymerase I. Specifically, Komori et al teach a number of *Pfu* DNA polymerase mutants which affect both the DNA polymerizing and/or the 3'-5' exonucleolytic activity in varying amounts. Komori et al. specifically teach mutant *Pfu* DNA polymerases in which the Asp 405 has been replaced by alanine, D405A, and glutamate, D405E. Each of these mutants have a greater than 100-fold and greater than 20-fold decrease, respectively, in the polymerizing activity of the mutant DNA polymerase, relative to the wildtype *Pfu* DNA polymerase. These mutants further have an approximate 10-fold decrease in the exonuclease activity. Thus each of the mutants created by Komori et al. have an approximate 50-fold and 2-fold increase, respectively, in the ratio of 3'-exonucleolytic activity to polymerizing activity relative to the wildtype *Pfu* DNA polymerase.

One of ordinary skill in the art at the time of filing would have been motivated to use either of the *Pfu* DNA polymerase mutants, D405A and D405E, taught by Komori et al. in the formulation taught by Barnes et al. to catalyze the amplification by PCR of unusually long and faithful DNA products. One would have been further motivated to include in the above formulation a PCR enhancing factor or an additive, as the purpose of the taught formulation is for

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PCR and package this formulation as a kit. The motivation for using the *Pfu* DNA polymerase mutants taught by Komori et al. comes from Barnes who teach that the thermostable DNA polymerase exhibiting 3'-exonuclease activity of the DNA polymerase formulation is preferably a variant of the *Pfu* DNA polymerase, wherein the DNA polymerase activity of said *Pfu* DNA polymerase has been diminished or inactivated. The mutants taught by Komori et al. are such variants of the *Pfu* DNA polymerase, wherein the DNA polymerase activity of said *Pfu* DNA polymerase has been diminished or inactivated. The reasonable expectation of success is high as both Barnes and Komori et al. teach a number of thermostable DNA polymerases for use in the taught formulation, and Komori et al. specifically teach the *Pfu* DNA polymerase, wherein the DNA polymerase activity of said *Pfu* DNA polymerase has been diminished or inactivated. It is acknowledged that the mutant *Pfu* DNA polymerases taught by Komori et al. in addition to having a diminished or inactivated DNA polymerase activity also have a reduced 3'-exonucleolytic activity, however as the specific mutants taught by Komori et al. actually have an increase in the ratio of 3'-exonucleolytic activity to DNA polymerizing activity, they would remain useful in the formulation of Barnes, as the presence of the 3'-exonucleolytic activity is the reason for addition of the second DNA polymerase of the formulation. This is further supported by the teachings and claims of Barnes who teach that the ratio of the "polymerase without 3'-exonucleolytic activity" to the "polymerase with 3'-exonucleolytic activity, wherein the polymerase activity is reduced or diminished" is high (i.e. from 10 to 2000 units to 1 unit), suggesting that the only functional property of the

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second polymerase that is important is the presence of the 3'-exonucleolytic activity, and that based on the ratios of the taught polymerase formulations, a slight decrease in the level of 3'-exonucleolytic activity can be accounted for by adjusting the ration of polymerases to remain within the level suggested by Barnes.

It is noted that this is a similar rejection to that originally made on 6/18/2003, and dropped on 10/19/2005. Applicant's amendment of the claims has resulted in the current rejection.

Thus, claims 64-66, 68, 71, 73, 75, 79, 85, 87, 89, 91 and 93 made obvious over Barnes et al. and Komori et al.

### ***Double Patenting***

Applicants comments in response to the previous statutory type double patenting rejection regarding the canceling of the subject matter of claims 1-3, 6, 9-11, 13-15, 19 and 21-23 are acknowledged, however it is further acknowledged that applicants along with the cancellation of claims 1-3, 6, 9-11, 13-15, 19 and 21-23, applicants added new claims 64-87 drawn to overlapping subject matter, thus necessitating a provisional nonstatutory double patenting rejection.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

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A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 64-94 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 6, 9-14, 18, 20-22 and 36-51 of copending Application No. 10/035,091. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed enzyme mixtures of the instant application, comprising a first enzyme and a second enzyme wherein said first enzyme comprises a Archaeal DNA polymerase and said second enzyme is a mutant Archaeal DNA polymerase comprising a 3'-5' exonuclease activity and a reduced polymerization activity and having a mutation at an amino acid position selected from the group consisting of D405, Y410, T542, K593, Y595, Y385, Y387, and G388 and those further limited claims dependent thereon are anticipated by and thus obvious over the corresponding claims of copending Application No. 10/035,091, drawn to a enzyme mixture comprising a first enzyme and a second enzyme wherein said first enzyme comprises a DNA polymerization activity and said second enzyme is a mutant Pfu DNA polymerase having a mutation at an amino acid position selected from the group consisting of D405, Y410, T542, K593, Y595, Y385, Y387, and G388 and those further limited claims dependent thereon.

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This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant acknowledgment of this provisional rejection is acknowledged, as well as applicant's statement of their intent of filing a terminal disclaimer as a means of overcoming the rejection at the time at which the claims are found otherwise allowable.

### ***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

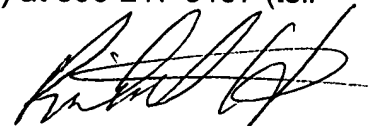
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number

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is (571) 272-0930. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Richard G Hutson, Ph.D.  
Primary Examiner  
Art Unit 1652

rg  
10/26/2006